REMARKS

In view of the above amendments and the following remarks, the Examiner is respectfully requested to withdraw the rejections, and allow claims 1, 3-5, 13, 15 and 16, the currently pending claims. Claims 2, 6-12, 14 and 17-18 have been canceled, without prejudice to refiling. Claims 1, 3, 5, 13, 15 and 16 have been amended. No new matter is added.

Support for the amending language "reentry into the mitotic cycle" may be found in the specification on page 5. line 29. Support for the amending language "prior to or during fertilization" may be found in the specification on page 8, line 24; and page 12, line 16-17.

A sequence listing in computer readable and in paper form is provided herewith.

Claims 1-5, 8, 9 and 13-18 have been rejected under 35 U.S.C. 112, second paragraph. Claims 1, 8 and 9 said to be rendered indefinite by the phrase "administering". Independent claims, 1 and 5 have been amended to recite a "contacting" step.

Claims 2, 15 and 17 are stated to be rendered indefinite by the phrase "in combination with" fertilization or nuclear transfer because it is unclear whether a modulator of nitric oxide in brought into contact with an oocyte before or after the event as intended. Claims 2 and 17 are canceled. Claims 5 and 15 have been amended to recite that in order to enhance activation, the sperm is brought in contact with the oocyte prior to or during activation. In order to inhibit activation, the NOS inhibitor is brought into contact with the oocyte prior to or during fertilization.

Claims 5 and 8 are stated to be rendered indefinite by the use of abbreviations. Throughout the claims the terms NO and NOS have been replaced with "nitric oxide" and "nitric oxide synthase".

In view of the above amendments and remarks, Applicants respectfully submit that the present claims meet the requirements of 35 U.S.C. 112. Withdrawal of the rejections is requested.

The present invention is based on the finding that NOS and nitric-oxide-related bioactivity are necessary and sufficient for activation of an oocyte during the process of fertilization. These findings were of such importance that the results were published in Nature, a highly prestigious journal.

Claims 1, 2, 8, 9, 14 and 15 have been rejected under 35 U.S.C. 102(b) as anticipated by Grumetto *et al*. Applicants respectfully submit that Grumetto *et al*. does not anticipate the present invention. The claims have been amended to recite the activation of oocytes, which is manifested by reentry into the mitotic cycle, as described in the specification

Grumetto *et al*. disclose the addition of sodium nitroprusside to ascidian *Ciona intestinalis* oocytes. Although the paper describes the generation of inward currents following such treatment,

oocyte activation was absent. In fact, as stated by the authors, the inward currents induced by SNP addition were not followed by production of the first polar body. The reference teaches away from the present invention, by stating that "SNP is not sufficient for oocyte activation". The reference therefore fails to teach or suggest the presently claimed method.

Claims 1, 2, 3, 8, 10, 11, 14 and 15 have been rejected under 35 U.S.C. 102(b) as anticipated by Jawerbaum *et al*. Jawerbaum disclose a method of modulating activation of oocytes comprising the step of contacting *in vitro* cultured and matured rat oocytes with a modulator of nitric oxide levels. Applicants respectfully submit that the present invention is not anticipated by Jawerbaum *et al*.

Jawerbaum *et al*. disclose the contact of an oocyte with NO donor or an NOS inhibitor. However, the reference fails to teach the inhibition of activation during fertilization, or the activation of the oocyte. The reference discloses that NO donors increase the production of prostaglandins , while inhibition of NOS decreases the accumulation of prostaglandins. However the reference fails to teach the activation of oocytes, or the inhibition of activation. There is no clear link between prostaglandin production and oocyte activation. One of skill in the art would not be in possession of the claimed invention, based on the teachings of the prior art. As set forth in Claims 1 and 5, the present invention is specifically directed preventing activation, or activating the oocyte to reenter the mitotic cycle, which methods are absent from the prior art.

In view of the above amendments and remarks, Applicants respectfully submit that the presently claimed invention meets the requirements of 35 U.S.C. 102. Withdrawal of the rejections is requested.

Claims 1-5, 8, 9 and 13-18 have been rejected under 35 U.S.C. 103(a) as unpatentable over Grumetto *et al.* in view of Jawerbaum *et al*., and U.S. Patent no. 6,077,710. Applicants respectfully submit that the presently claimed invention is not made obvious by the cited combination of art.

As discussed above with respect to the primary references, the art does not teach how one could achieve oocyte activation, or prevent oocyte activation, through contact with NO or NO inhibitors. There is no clear connection between the inward currents of Grumetto *et al.*, or the prostaglandins of Jawerbaum *et al*, and the reentry into mitotic cycle found by Applicants.

The secondary reference fails to remedy the deficiencies of the primary references. U.S. 6,077,710 teaches oocyte activation by introducing Ca^{+2} free cation in combination with a serine threonine kinase inhibitor. The reference is silent on the subject of NO donors and inhibitors, and therefore provides no guidance that would enable one of skill in the art to practice the present

invention. Even when taken in combination, the art fails to provide a reasonable expectation of success for the claimed methods.

In view of the above amendments and remarks, Applicants respectfully submit that the invention as presently claimed meets the requirements of 35 U.S.C. 103. Withdrawal of the rejection is requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned **"Version with Markings to Show Changes Made."**

CONCLUSION

Applicants submit that all of the claims are now in condition for allowance, which action is requested. If the Examiner finds that a Telephone Conference would expedite the prosecution of this application, she is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any other fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number STAN209.

Respectfully submitted,

Date: September 13, 2001

By: Pamela Sherwood
Pamela J. Sherwood, Ph.D.
Registration No. 36,677

BOZICEVIC, FIELD & FRANCIS LLP
200 Middlefield Road, Suite 200
Menlo Park, CA 94025
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claim 1 has been amended as follows:

1. (amended) A method of [modulating] activating an oocyte *in vitro* [activation], the method comprising:

[administering] contacting [a modulator of nitric oxide levels to] said oocyte with nitric oxide (NO), an NO donor, nitric oxide synthase (NOS), or inducer of NOS;

wherein said oocyte is activated to reenter the mitotic cycle.

Claim 2 has been cancelled.

Claim 3 has been amended as follows:

3. (amended) The method according to Claim [2] 1, wherein said oocyte is a mammalian oocyte.

Claim 5 has been amended as follows:

5. (amended) A method of inhibiting oocyte activation during fertilization *in vitro*, the method comprising:

[The method of Claim 2, wherein said modulator of nitric oxide levels is] contacting said oocyte with a nitric oxide synthase [NOS] inhibitor prior to or during fertilization;

[and wherein said administering step prevents oocyte activation]

wherein said oocyte is inhibited from activation and reentry into the mitotic cycle.

Claims 6-12 have been cancelled.

Claim 13 has been amended as follows:

13. (amended) The method of Claim [11] 5, wherein said oocyte is a human oocyte.

Claim 14 has been cancelled.

Claim 15 has been amended as follows:

15. (amended) The method according to Claim [14] 1, further comprising the step of contacting said oocyte with sperm prior to or during said activation[, wherein said activation is performed in combination with fertilization].

Claim 16 has been amended as follows:

16. (amended) The method according to Claim 1 [14], wherein said activation [provide parthenogenetic activation] is performed in the absence of sperm.

Claims 17 and 18 have been cancelled.